## *Remarks*

Reconsideration of this Application is respectfully requested.

Upon entry of the forgoing amendments, claims 27-75 are pending in the application. Claims 47-75 are sought to be added. Support for the new claims can be found throughout the specification and original claims. For example, support can be found in the specification at page 32, lines 1-14; page 33, lines 14-24; page 35, line 17 to page 18, line 4; page 24, lines 18-21, and page 27, line 23 to page 28, line 19. The amendments are believed to introduce no new matter and entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

### *Claim Rejections Under 35 U.S.C. § 101*

The Examiner has rejected claims 27-46 under 35 U.S.C. § 101 because allegedly, "the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well established utility." (Paper No. 19, page 2.) For the following reasons, Applicants respectfully disagree and traverse the Examiner's rejection.

Initially, the Examiner is reminded that Applicants need only provide one credible assertion of specific and substantial utility for the claimed invention to satisfy the utility requirement. (Federal Register, Vol. 66, No. 4, Friday, January 5, 2001, 1098.) "When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown." *Raytheon v. Roper*, 724 F.2d 951, 958 (Fed. Cir. 1983). According to the

M.P.E.P., a specific utility is specific to the subject matter claimed, in contrast to a utility that would be applicable to the broad class of the invention. A substantial utility defines a "real world" use. (M.P.E.P. § 2107.01(I).) For example, a therapeutic method of treating a known of newly discovered disease has a substantial utility and defines a "real world" use. (*Id.*)

Applicants assert that the claimed invention has at least one specific and substantial asserted utility. The specification teaches that the claimed polypeptides can, among other things, be used to generate agonists of DR3-V1 and DR3. *Such a utility does not require identification of a ligand.* An agonist is defined as an agent, e.g. an antibody, which is capable of increasing DR3-V1 or DR3 mediated signaling. (Specification, page 6, lines 1-5; page 39, lines 3-7.) Preferably, DR3-V1 or DR3 mediated signaling is increased to treat a disease wherein decreased apoptosis is exhibited. (*Id.* at page 39, lines 7-11.) According to the specification, a specific disease where decreased apoptosis is exhibited is autoimmune disease. (Page 38, lines 18-21.) Moreover, the specification states that:

> Apoptosis-programmed cell death-is [sic] a physiological mechanism involved in the deletion of peripheral T lymphocytes of the immune system, and its dysregulation can lead to a number of pathogenic processes.

(Page 38, lines 13-16.) The specification also teaches that DR3-V1 can be envisaged as playing a role in lymphocyte homeostasis. (Page 62, lines 20-21.)

The use of the claimed polypeptides to generate DR3-V1 and DR3-specific agonists, e.g., agonistic antibodies, is a specific utility not applicable to the broad class of the invention—i.e., not all polypeptides can be used to generate DR3-V1 and DR3-specific agonists. (*See* M.P.E.P. § 2107.01 (I).) Further, the use of the claimed polypeptides to generate specific agonists is a substantial utility, as the treatment and prevention of

autoimmune diseases, and diseases associated with the T lymphocyte disregulation and lymphocyte homeostasis constitute "real world" utilities. (*See* M.P.E.P. § 2107.01 (I).) Accordingly, the claimed proteins have a specific and substantial utility.

Based, in part, on the homology of the claimed polypeptides to TNF R1 and Fas (Figure 3A-3D), the tissue distribution of DR3-V1 gene expression (Example 4) and the confirmed biological activity of DR3 (Example 6), one of ordinary skill in the art would find the asserted utilities credible and "more likely than not" true.

However, in case the Examiner has doubts about the credibility of Applicants' assertions, Applicants submit herewith two publications, Tartaglia & Goeddel, *J. Biol. Chem.* 267: 4304-4307 (1992) (Exhibit A) and Wang *et al.*, *Mol. Cell. Biol.* 21: 3451-3461 (2001) (Exhibit B), and a poster produced by the assignee and a collaborator entitled "TRM-1, A Human TRAIL-R1 Agonistic Monoclonal Antibody, Displays In Vitro and In Vivo Anti-tumor Activity" by Salcedo *et al.* (attached as Exhibit C). The publications and poster provide support that the following assertions are credible:

(A) Agonistic antibodies against DR3-V1 and DR3 can be utilized to trigger DR3 and/or DR3-V1 meditated signaling; and

(B) Agonistic antibodies against DR3-V1 and DR3 can be utilized to treat and/or prevent specific disorders, e.g., autoimmune diseases and diseases associated with lymphocyte homeostasis and T-cell dysregulation.

Tartaglia & Goeddel state that "[b]oth polyclonal and monoclonal antibodies directed against human TNF-R1 have been shown to behave as receptor agonists and elicit several TNF activities such as cytotoxicity, fibroblast proliferation, resistance to chlamydiae and synthesis of prostoglandin $E_2$." (Tartaglia & Goeddel at 4304, column 2 (citations

removed).) In their own experiments, Tartaglia & Goeddel show that the 55-kDa TNF receptor, stably expressed in mouse L929 cells, was activated specifically by agonist antibodies and initiated the signal for cellular cytotoxicity. (*Id.* at column 1.)

Salcedo *et al.*, also studying agonistic antibodies of TNF receptors, found that TRM-1, a human agonistic antibody specific for TRAIL R1, induced apoptosis in human cancer cell lines *in vitro* and reduced tumor growth in human colon and uterine xenograft models in nude mice. (*See* Conclusions, columns 5-6.) In addition, TRM-2, a human agonistic antibody specific for TRAIL R2, was found to be effective in reducing or preventing tumor growth in human colon xenograft models in nude mice. (*Id.*) As the claimed polypeptides are also members of the apoptosis-inducing subfamily of TNF family of receptors studied by Tartaglia & Goeddel and Salcedo *et al.*, Applicants submit that the teachings of Tartaglia & Goeddel and Salcedo *et al.* support the assertion that agonistic antibodies of the claimed polypeptides can be used to trigger DR3-V1 and/or DR3 activity.

The Examiner's attention is further directed to the teachings of Wang *et al.*, which further provides support that agonistic antibodies of DR3-V1 and DR3 can be used to treat and/or prevent specific diseases and disorders. Specifically, Wang *et al.* studied the *in vivo* role of DR3 by generating mice congenitally deficient in the expression of the DR3 gene. (Wang *et al.*, page 3451, abstract.) They show that negative selection and anti-CD3 -induced apoptosis are significantly impaired in DR3-null mice. (*Id.*) Wang *et al.* indicate that, in contrast, both superantigen-induced negative selection and positive selection are normal. (*Id.*) Further, they show that the pre-T-cell mediated checkpoint, which is dependent on TNFR signaling, is also unaffected in DR3-deficient mice. (*Id.*) Wang *et al.* conclude that:

> [t]hese data reveal a nonredundant in vivo role for this TNF receptor family member in the removal of self-reactive T cells in the thymus.

(*Id.*) Thus, Wang *et al.* provide support that agonists of the claimed polypeptides can be used in the treatment and/or prevention of, for example, autoimmune diseases, diseases associated with lymphocyte homeostasis and T-cell dysregulation, as asserted in the specification and discussed above.

With respect to the utility of the claimed proteins to generate agonistic antibodies of DR3 and/or DR3-V1, the Examiner has stated that "there is not a single example of record, either in the specification or the art of record, of the successful administration of an agonist antibody for clinical effect." (Paper No. 19, page 3.) In response, Applicants note that actual examples or data generated from clinical trials need not be provided to satisfy the utility requirement. (M.P.E.P. § 2107.03(IV).) All that is required of a statement of utility is that it be "reasonably predictive." *See, e.g.*, *Rey-Bellet v. Englehardt*, 493 F.2d 1380 (C.P.P.A. 1974). If reasonably correlated to the particular therapeutic or pharmacological activity, data generated using *in vitro* assays, or from testing in an animal model or combination thereof *almost invariably* will be sufficient to establish a therapeutic or pharmacological utility for a compound, composition or process. (M.P.E.P. § 2107.03(III) (emphasis added).) In view of all the evidence on record, including the confirmed biological function of the claimed polypeptides provided in Examples 5 and 6, Applicants submit that it is "reasonably predictive" that the claimed polypeptides can be used to generate agonistic antibodies of DR3-V1 and DR3 for the treatment and/or prevention of autoimmune disease and diseases associated with lymphocyte homeostasis and T-cell dysregulation.

The Examiner also appears to suggest that *selective* killing of malignant cells is

required for the agonistic antibodies of the claimed invention to be effective. (Paper No. 19, page 3.) Applicants respectfully disagree.

It is well known in the art that many cancer drugs are non-selective and kill not only tumor cells, but also normal, healthy cells. It is also well known that the administration of other types of drugs for the treatment of other types of diseases is often accompanied by significant, deleterious side effects. Yet, these drugs are still considered useful. As with any drug, the scientist must utilize a cost-benefit analysis to determine whether or not the good caused by the drug outweighs the harm. Considerations such as dosage amounts, treatment periods, methods of administration, and co-administration with other drugs factor into the cost-benefit analysis and can be manipulated in order to ensure maximum benefit of a drug, while minimizing any harmful effects in the patient.

Further, Applicants note that there are certain cancer and/or tumor treatments which do, in fact, involve killing *all* lymphocytes as exemplified by autologous transplantation techniques for the treatment of cancers. The International Society for Stem Cell Research, for example, defines autologous transplantation as follows:

> Cell, tissue, or organ transplants from one person back to the same person. Such transplants from self do not induce an immune response and are not rejected. In one example, a cancer patient may have her HSC or bone marrow removed and stored during treatment *with sufficient radiation or chemical therapy to kill all blood-forming cells* (and, perhaps, all cancer cells), and then her blood-forming capacity is rescued with autologous HSC or bone marrow.

(International Society for Stem Cell Research: Definitions *at* http://tnt.tchlab.org/stemcells/definitions.htm) (emphasis added) (copy of website attached as Exhibit D).)

Aside from generating agonistic antibodies, one of ordinary skill in the art would find

it reasonable to believe that soluble forms of the claimed proteins are also useful for therapeutic purposes. For example, the specification states that:

> [S]oluble forms of the receptor, which may be naturally occurring or synthetic, antagonize DR3-V1 or DR3 mediated signaling by competing with the cell surface DR3-V1 or DR3 for binding to TNF-family ligands. Thus, soluble forms of the receptor that include the ligand binding domain are novel cytokines capable of inhibiting apotosis induced by TNF-family ligands. These are preferably expressed as dimers or trimers, since these have been shown to be superior to monomeric forms of soluble receptor as antagonists.

(Page 43, lines 12-18.) Thus, Applicants argue that one utility of the instant invention lies in the effect that the soluble receptor will have on endogenous DR3-V1 and DR3 receptors or available ligands of DR3-V1 and DR3. In this use, administration of the isolated polypeptides of the claimed invention can regulate apoptosis by interacting with endogenous receptor, or binding free ligand, thereby preventing the ligand from binding endogenous receptors and triggering apoptosis.

In support of this utility, Applicants direct the Examiner to Migone *et al.*, *Immunity* 16: 479-492 (2002) (Exhibit E). Migone *et al.* not only identify the ligand of DR3 as TL1A, they also indicate that TR6, a TNFR family member lacking a cytoplasmic domain, acts as a "decoy" receptor and may act as an inhibitor of apoptosis by competing with the signal tranducing receptor for the ligand. Similarly, providing excess soluble receptor of the claimed proteins could conceivably function in the same way as the known "decoy" receptor (TR6) by competing for TL1A. To that end, the specification teaches the relevant structural regions (extracellular, intracellular, and transmembrane domains) of the claimed proteins at, for example, page 14, lines 12-19.

Applicants have submitted, in a Reply dated November 21, 2001, an example of a

soluble TNF receptor being used as a pharmaceutical in manner similar to the decoy receptor utility described above. Enbrel™ is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor. Enbrel™ works by binding specifically to TNF and blocking its interaction with cell surface receptors, rendering TNF biologically inactive. One of ordinary skill in the art would find it credible that the claimed invention could be used in a similar fashion.[1]

In view of the above, it is clear that at least one asserted utility of the claimed polypeptides is specific, substantial and credible. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

***Claim Rejections Under 35 U.S.C. § 112, First Paragraph***

The Examiner has maintained his rejection of claims 27-46 under 35 U.S.C. § 112, first paragraph. The Examiner contends that since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well-established utility, for the reasons above with regards to the rejection under 35 U.S.C. § 101, one skilled in the art would not know how to use the claimed invention. (Paper No. 19, page 6.)

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[1] The Examiner has stated that "Applicant's reliance on *In re Brana* is misplaced." (Paper No. 19, page 2.) Specifically, the Examiner has asserted the "protein of the instant invention does not belong to a family of compounds with a common well established specific and substantial utility." (*Id.*) Applicants respectfully disagree. Contrary to the Examiner's assertions, the claimed protein is, in fact, a member of a class of compounds with an established utility—i.e., it is a member of the TNF receptor family. As discussed here and in the previous reply, members of the TNF receptor family have been shown to have a specific and substantial utility as evidenced by the product Enbrel™, which is derived from a TNF receptor and used for the treatment of rheumatoid arthritis (RA). Tenefuse™ is another product derived from a TNF receptor that has been studied to treat RA. *See, e.g.*, Gardnerova *et al.*, *Curr. Drug. Targets* 1: 327-364, 334-335 (2000) (Exhibit F.) Accordingly, Applicants submit that *In re Brana* supports Applicants' assertions of utility.

In view of the above, the claimed invention has a patentable utility under 35 U.S.C. § 101. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." (M.P.E.P. § 2107(IV) at 2100-28.) Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

***Claim Rejections Under 35 U.S.C. § 102(b)***

The Examiner has rejected claims 27-46 under 35 U.S.C. § 102(b) as allegedly being anticipated by each of the Chinnaiyan *et al.*, *Science* 274:990-992 (1996) and Kitson *et al.*, *Nature* 384:372-375 (1996). (Paper No. 19, page 6.) In short, the Examiner contends that these publications are prior art because the priority applications of the present case are unavailable under 35 U.S.C. § 120. The Examiners' rationale is that because the present application doesn't meet the requirements of 35 U.S.C. § 112, first paragraph, the prior applications also do not meet this requirement. Applicants respectfully traverse this rejection.

As discussed above, Applicants believe that the requirements of 35 U.S.C. § 112, first paragraph, have been satisfied for the present application. The requirements of 35 U.S.C. § 112, first paragraph, have also been satisfied for the earlier priority applications. Accordingly, Applicants submit herewith that the Chinnaiyan *et al.* and Kitson *et al.* publications are not available as prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

***Request for an Interview***

Applicants believe that the above discussion properly traverses, accommodates, or renders moot all of the stated grounds of objection and rejection. However, in the event that the Examiner disagrees and maintains the rejections, Applicants respectfully request that an interview be granted with the undersigned prior to issuance of another Office Action or Advisory Action.

## *Conclusion*

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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## Version with markings to show changes made

The application has been amended as follows:

***In the Claims:***

Claims 47- 75 have been newly added.